IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

APOTEX, INC., Plaintiff,	:	CIVIL ACTION
v.	:	No. 2:06-cv-2768
CEPHALON, INC., et al., Defendants.	:	

Goldberg, J. **March 28, 2012**

MEMORANDUM OPINION

This opinion addresses whether Plaintiff, Apotex, Inc.'s, abbreviated new drug application number 77-667 (the "ANDA")[1] infringes Defendant, Cephalon, Inc.'s, United States Patent, No. RE37,516 (the "RE '516 patent"). After careful consideration of the evidence presented at a bench trial, the Court finds that Cephalon has failed to demonstrate, by a preponderance of the evidence, that the product Apotex is likely to manufacture pursuant to its ANDA will infringe the RE '516 patent.

I. Introduction

As detailed in prior Opinions, the patent dispute between Apotex and Cephalon is one of several cases currently consolidated under the caption In re Modafinil. This particular case was initiated on June 26, 2006, when Apotex filed its complaint raising patent claims regarding Cephalon's RE '516 patent for Provigil®, a pharmaceutical composition comprised of modafinil in the form of particles of a defined size. The complaint also set out antitrust claims against Cephalon

[1]Apotex's ANDA was originally submitted on March 30, 2005, and subsequently modified on July 12, 2010. (PTX 301; Stip., Doc. No. 438.) We therefore consider the question of infringement in light of these modifications.

and four generic drug companies. Apotex subsequently filed amended, and second amended complaints, moving for a declaratory judgment that the RE '516 patent is invalid, unenforceable and not infringed by the generic form of Provigil® described in Apotex's ANDA.

Apotex's invalidity and unenforceability claims were bifurcated from its non-infringement claim. A bench trial on the claims of invalidity and unenforceability was held from March 29 to April 7, 2011, and the Court subsequently concluded that the RE '516 patent was both invalid and unenforceable. The second bench trial, on Apotex's non-infringement claim, which is the subject of this Opinion, was held from July 12 to 20, 2011.

The infringement dispute essentially concerns the size of the modafinil particles which make up the pharmaceutical compositions described in Cephalon's RE '516 patent and Apotex's ANDA. Aside from the dispute relating to particle size, the parties agree that the product described in the ANDA meets all of the claim limitations in the RE '516 patent. (See , e.g., N.T. 7/13/2011, pp. 110-11.) Particle size is therefore central to the question of infringement, and was the principal claim of the RE '516 patent that Cephalon claimed to be innovative. (See Am. Invalidity Mem. Op., Doc. No. 516, p. 17, Fact 80.)

Pursuant to the Court's claim construction, the patent at issue claims a pharmaceutical composition of modafinil wherein at least 95% of the modafinil particles have a diameter of less than 220 microns (μm).[2] The particle size specification in Apotex's ANDA requires that only 25-80% of the modafinil particles have a diameter of less than 220 μm. Thus, when Apotex's accused device is compared to the claimed RE '516 particle size, it appears that the ANDA does not infringe.

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[2]A micron is "a unit of length equal to one millionth of a meter." OXFORD ENGLISH DICTIONARY (Oxford University Press, April 2010).

Cephalon disagrees and argues that Apotex's specification does not answer the question of infringement because it applies to the API[3] rather than to the final tablets to which the limitations in the patent apply. Cephalon stresses that after the particle size of the API is measured, the manufacturing process described in the ANDA dictates that the modafinil undergo a milling step called "comilling."[4] Cephalon thus asserts that comilling reduces particle size so that the pharmaceutical composition described in Apotex's ANDA falls within the particle size limitation of the RE '516 patent. As evidence of the effect of comilling, Cephalon asks the Court to consider particle size testing that it conducted on a modafinil product that Apotex currently sells in Canada. Cephalon posits that the Canadian product is representative of what Apotex is likely to produce pursuant to its ANDA, and that the testing demonstrates that at least 95% of the modafinil particles in the Canadian tablets have a diameter of less than 220 μm.

Apotex responds that the particle size specification in its ANDA directly addresses the question of infringement, and in fact renders infringement "mathematically impossible." Further, although Apotex admits that the comilling step has the potential to reduce particle size, it asserts that there is no evidence that the reduction is significant, let alone enough to bring the final product within claims of the RE '516 patent. Regarding Cephalon's testing of its Canadian product, Apotex argues that the method used by Cephalon to isolate and measure the particle size is unreliable, that the results show too great a variance to demonstrate infringement, and that, in any event, the

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[3]"API" is an acronym for "Active Pharmaceutical Ingredient," and refers to the bulk powder form of the active ingredient that ultimately goes into a tablet approved for sale. (N.T. 7/13/2011, p. 148 (Antonietti).)

[4]The term "comilling" is derivative of the type and brand of mill that is used in the ANDA's manufacturing process - a conical "Quadro Comil."

Canadian product is irrelevant because it was produced pursuant to a specification that differs significantly from the particle size specification in the ANDA.

II. Background

A. The RE '516 Patent

The RE '516 patent issued on January 15, 2001, as a reissue of U.S. Patent No. 5,618,845 ("the '845 patent"). (Am. Invalidity Mem. Op., Fact 9.) Entitled "Acetamide derivative having defined particle size," the RE '516 patent contains twenty-six claims and is "designed to cover modafinil of a certain particle size" in order to produce "a predictable bioavilability and potency in humans." (Markman Op., Doc. No. 335, p. 2.) Cephalon has asserted that the Apotex ANDA infringes claims 1-14 and 16 of the RE '516 patent. (Stip. No. 11, Doc. No. 438.) In pertinent part, the patent claims "[a] pharmaceutical composition comprising a substantially homogeneous mixture of modafinil particles, wherein at least 95% of the cumulative total of modafinil particles in said composition have a diameter less than about 200 microns (μm)." (JTX 1.)

The parties largely agreed on the meaning of the particle size limitation in Cephalon's patent, and that it covers a "pharmaceutical composition," meaning the final tabletted form of a drug that is ready for sale. Further, they agreed that the novel aspect of the patent is its particle size limitation, and that "about 200 microns" allows for a margin of error of approximately 10%, meaning that the claim can be met if the requisite number of modafinil particles are smaller than 220 μm, rather than 200 μm. However, the parties disputed what "95% of the cumulative total of modafinil/said particles" encompassed, and how diameter and size distribution of the particles were to be

measured.[5]

Accordingly, the Court held a claim construction hearing pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370, 788-91 (1996), to resolve those disputes. In our October 6, 2010 Opinion, we determined that, based upon the patent's language and its prosecution history, the particle size specification referred to all of the measurable particles of modafinil contained in the pharmaceutical composition, and that the patent allowed particle size to be measured by any conventional method. Under this construction, the pertinent claim for purposes of the alleged infringement is a tablet of modafinil wherein at least 95% of the cumulative total of all of the measurable particles of modafinil are less than 220 μm in diameter, as measured by any conventional method.

B. The ANDA

The Hatch-Waxman Act of 1984 created the ANDA, which allows a generic drug application to piggyback on safety and efficacy studies conducted for a pioneer drug. See generally 21 U.S.C. § 355(j). This Act was designed to allow generic companies to bypass the studies required under a New Drug Application ("NDA") and file an ANDA, which requires only that generic companies show that the new drug is the bioequivalent of a brand name drug on the market. Id. § 355(j)(2)(A). Under the Act, an ANDA filer must select one of four certifications with regard to any patents that cover the brand name drug. A "Paragraph IV" certification asserts "that such patent is

[5]The parties also disputed whether the definition of "particle" included agglomerates. At the Markman hearing the parties agreed that the definition used in the patent—"a piece or grain of modafinil"—was an acceptable claim construction. The Court was unable to determine whether this definition included agglomerates because the claim language, specification and prosecution history are silent on the issue, and the expert testimony submitted by the parties did not even consistently define the term agglomerate. We continue to find it unnecessary to resolve this issue because it has no bearing on the question of infringement.

invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." Id. § 355(j)(2)(A)(vii). The filing of an ANDA Paragraph IV certification is considered a technical act of infringement and allows the patent holders to sue the ANDA filer within forty-five days of receipt of the certification.

Apotex originally filed its ANDA on March 30, 2005. Included as part of the ANDA was a description of the manufacturing process Apotex proposed to use for its generic modafinil product, a specification for the particle size of the modafinil and particle size testing it had conducted on sample of modafinil API.[6] With regard to particle size, the 2005 ANDA required that at least 20% of the modafinil particles be less than 250 µm in diameter, as measured by sieving. (JTX-5-0119; ANDA-MOD-138.) While the ANDA itself did not contain an upper limit on the percentage of modafinil particles that could be smaller than 250µm in diameter, two types of particle size testing conducted on the biobatch—sieving and laser diffraction—indicated that fewer than 95% of the modafinil particles were below that threshold, at least prior to undergoing the manufacturing process. (ANDA-MOD-336.) Sieving of three samples indicated that only 31-38% passed through a sieve with 250-micron holes. (Id.) Laser diffraction similarly indicated that between 24.87% and 30.07% of particles, by volume, were smaller than 250 µm. (Id. at 337.)

On July 12, 2010, Apotex filed a gratuitous amendment to its ANDA, modifying the particle size specification so as to provide an upper limit on the percentage of modafinil particles that could be smaller than 250 µm in diameter. (PTX 301.) Under the modified specification, no less than 25%, and no more than 80%, of particles are permitted to pass through the 250-micron sieve. (Id.)

[6]The sample of a drug which is tested and tabletted for purposes of the ANDA process is referred to as the "biobatch." Bayer v. Elan Pharm. Research Corp., 212 F.3d 1241, 1246 (Fed. Cir. 2000).

As Cephalon points out, under Apotex's ANDA, measurement of modafinil particle size is conducted on the API powder, prior to the manufacturing and tabletting processes. Cephalon argues that during the manufacturing process, particle size is reduced to a sufficient degree so as to bring the final tablet within the claims of the RE '516 patent. In particular, Cephalon's argument is focused upon the first step in the manufacturing process, the "milling" step. This step requires that the modafinil API pass through a Quadro Comil No. 196, which is a cone-shaped filter with holes that are 450 μm in diameter, fitted with two rounded impellers that spin around the inside of the filter at 900 RPM. (N.T. 7/13/2011, p. 151 (Antonietti); DDX 6-01.)

While Apotex admits that the milling step has the potential to reduce particle size, the degree to which this occurs under these particular circumstances is disputed by the parties, and was a topic of expert testimony at trial. Dr. Marcus Antonietti, who was called to testify on behalf of Cephalon, offered the opinion that the milling step was "likely to result in a particle size distribution in which 95 % of the modafinil particles have a diameter of less than 220 microns." (Id., p. 173.) His opinion was based upon his knowledge of milling principles, the characteristics of modafinil particles, his review of the ANDA and the Quadro Comil specifications, and the testing of Apotex's Canadian product performed by two other experts hired by Cephalon.

Apotex's expert, Dr. David Beach, testified that the main purpose of Apotex's milling step was to break apart modafinil particles that had stuck together, and that, considering the type of screen, and the type and speed of the impeller, there simply was not sufficient energy in the mill to reduce the size of modafinil particles enough to bring them within the claim. (N.T. 7/19/2011, pp. 50-57.) However, neither expert had actually run Apotex modafinil API through the Quadro Comil under the specifications described in the ANDA and subsequently measured the particle size

distribution. As such, neither expert could give a quantitative opinion as to the extent to which particle size would be reduced under those circumstances. Instead, Cephalon introduced evidence of particle size testing conducted on Apotex's Canadian product, which it contends demonstrates the effect of the milling step. Cephalon asserts that Apotex's Canadian product is representative of what is likely to be produced pursuant to the ANDA, and that its testing shows that the product will infringe the particle size claims of its patent.

C. The Canadian Testing

In August 2010, after failing to obtain unexpired samples of Apotex's biobatch, Cephalon independently obtained modafinil tablets sold by Apotex in Canada.[7] Cephalon purchased 100-mg modafinil tablets, which were given to Dr. Lynne Van Campen to separate and isolate the modafinil particles. Dr. Van Campen prepared six modafinil samples, and subsequently turned them over to Dr. David Bugay for particle size testing.

Dr. Van Campen was presented as an expert by Cephalon in "pharmaceutical development of drug products, specifically the physical and chemical aspects of drug formulation and manufacturing," and testified regarding the process she used to isolate the individual modafinil

[7]We note that Cephalon has moved for an adverse inference that Apotex's product would infringe the RE '516 patent based upon this failure to produce unexpired samples. Cephalon requested modafinil samples "meeting all specifications . . . described in the Apotex ANDA and capable of being offered for sale or sold in the United States upon final approval of the Apotex ANDA." Apotex responded that it had no such modafinil samples in its possession. Cephalon argues this was a misrepresentation because the Canadian tablets are identical to what would be produced pursuant to the ANDA. (Mot. for Adverse Inference, Doc. No. 468, pp. 3-4.) However, Apotex convincingly points out that the Canadian tablets were produced under a different specification and are certainly not capable of being offered for sale in the United States. In any event, Cephalon was able to obtain the Canadian tablets, and conducted extensive testing on that product prior to trial, ameliorating any potential prejudice resulting from Apotex's "misrepresentation." Under these circumstances, the sanction requested by Cephalon is unjustified and its motion will be denied.

particles in the Canadian tablets. (N.T. 7/12/2011, p. 78.)

First, Dr. Van Campen prepared six 200-mg samples by combining two of the 100-mg tablets in order to coincide with Apotex's ANDA, which sought approval for a 200-mg tablet. (Id., p. 98.) She then used a protocol on each of the samples that involved, among other things, sonication, a shaker bath and centrifugation. The protocol was designed to break down the tablet and isolate the modafinil particles from the other compounds based upon their densities. (Id., pp. 100-27.) Dr. Van Campen testified that her protocol effectively isolated the modafinil particles, and that very few of those particles were lost in the process. (Id., p. 102.) Dr. Van Campen further explained that she used Cephalon API of known particle size distribution to validate her protocol. (Id., pp. 123-24.) By subjecting some of the API to the isolation protocol, and then comparing its particle size distribution with the rest of the API that had not undergone the protocol, Dr. Van Campen testified that she could be confident that her protocol did not alter the particle size distribution. (Id., pp. 123-129.) It was therefore her opinion that the protocol effectively isolated the modafinil particles contained in a tablet without losing or destroying a significant number of particles, and without skewing the particle size distribution. (Id.) After Dr. Van Campen isolated the modafinil in each of the six samples, she turned them over to Dr. Bugay for particle size testing. (Id., pp. 129-30.)

Dr. David Bugay was presented by Cephalon as an expert in "physical and analytical chemistry," and, more specifically, in the measurement and analysis of pharmaceutical particle size. (N.T. 7/13/2011, pp. 14-15.) He testified that he received the isolated modafinil particles from Dr. Van Campen, and conducted a particle size analysis on those samples using a Hiac-Royco brand "light obscuration instrument." (Id., p. 17.) "Light obscuration" measures particle size by passing individual particles of a pharmaceutical substance between a light source and an electronic sensor.

The electronic sensor records the magnitude of light that is blocked by each of the particles and, based upon that reading, determines their size. (Id., pp. 22-23.) Dr. Bugay testified that the Hiac-Royco instrument that he used was factory calibrated using small spheres of standard size provided by the National Institute of Standards and Technology, and that it was re-calibrated prior to testing of the modafinil samples. (Id., pp. 25-29.) In order to test the samples provided by Dr. Van Campen, each sample was separated into three "preps," and each prep was put through the Hiac-Royco three times. Dr. Bugay then averaged the nine particle size results (three "preps" with three tests each) to obtain a particle size distribution for each of the six samples. The results of Dr. Bugay's testing is summarized in the following table:

Sample	50 % of Particles smaller than (µm)	95% of particles smaller than (µm)
1	124.14	221.7
2	84.27	285.0
3	60.98	268.2
4	46.83	158.9
5	49.99	199.9
6	51.07	200.9

(DTX-410)

Based upon these results, Dr. Bugay testified that for three of the six samples, 95% of the particles, by volume, were smaller than 220 µm. (N.T. 7/13/2011, p. 17.) According to Dr. Bugay, this demonstrated infringement because each sample, which represented a 200-mg tablet, should be considered a separate "pharmaceutical composition." (Id., p. 57.) Dr. Bugay explained that the difference in the results was due to variation in the composition of the samples, rather than any error in Dr. Van Campen's isolation protocol or his particle size measurements. (Id., pp. 44-46.)

Accordingly, Dr. Bugay opined that the particle size distribution in the Canadian tablets manufactured by Apotex met the claim limitations in the RE '516 patent.

Dr. Beach, who was tendered by Apotex as an "expert in measurement analysis and [the] use of particle size data," criticized the testing performed by Cephalon's experts. (N.T. 7/19/2011, p. 12.) He testified that he had never seen a protocol like the one used by Dr. Van Campen, or heard anyone claim to be able to extract particles from a tablet for accurate particle size measurement. (Id., p. 80.) According to Dr. Beach, several steps in the protocol would have skewed particle size distribution in the tablets, and he noted that Dr. Van Campen admitted that as much as 10% of the particles were lost during the protocol. (Id., p. 85.) Dr. Beach opined that the washing steps in particular had the potential to cause the loss of larger particles, and that such losses would have skewed the results toward a smaller particle size distribution. (Id., pp. 112-13.) He further testified that the protocol included three sonication steps, which had the potential to break apart the modafinil particles, further skewing the results toward smaller particle size. (Id., p. 91.) Ultimately, Dr. Beach testified that the various problems with Dr. Van Campen's protocol were demonstrated by the variation in the results of Dr. Bugay's particle size testing, both between the six samples, and between the nine different tests performed on each sample. (Id., pp. 96-103.) For these reasons, Dr. Beach opined that the particle size testing performed by Cephalon's experts was not reliable. (Id., p. 95.)[8]

[8]We note that Dr. Beach did not testify regarding the procedures and protocols used by Dr. Bugay in his use of the Hiac-Royco instrument. In fact, Apotex admitted at trial that it was not challenging this aspect of Dr. Bugay's testimony. (N.T. 7/13/2011, p. 27.) Accordingly, Cephalon's motion to preclude Dr. Beach's testimony regarding the Hiac-Royco, (Doc. No. 465), will be denied as moot.

III. Legal Standards

The determination of infringement requires that a court first construe the claims at issue to determine their scope and meaning, and then compare those claims to "the accused device or process." Caroll Touch, Inc. v. Electro Mechanical Sys., Inc., 15 F.3d 1573, 1576 (Fed. Cir. 1993). Whether a product infringes the claims of a patent is a question of fact on which the patentee bears the burden of proof by a preponderance of evidence. Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1467 (Fed. Cir. 1998). It is therefore Cephalon's burden to establish infringement, either literally or under the doctrine of equivalents. "Literal infringement requires the patentee to prove that the accused device contains each limitation of the asserted claim(s)." Bayer v. Elan Pharmaceutical Research Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000). If the product does not literally meet every limitation, "infringement may still occur under the doctrine of equivalents if there is not a substantial difference between the limitations of the claim and the accused product." Id. at 1250. In this case, Cephalon argues that the product Apotex will market upon approval of its ANDA will literally infringe the particle size claims in its patent.

Cephalon's claim arises under the infringement provision of the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A), which states that it is an act of infringement to submit an ANDA for "a drug claimed in a patent." Accordingly, "[t]he focus under § 271(e)(2)(A) is on 'what the ANDA applicant will likely market if its application is approved.'" Bayer AG v. Elan Pharm Research Corp., 212 F.3d 1241, 1248 (Fed. Cir. 2000) (quoting Glaxo v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997)).

IV. Discussion

The difficulty that can arise in an action under § 271(e)(2)(A) is that the alleged infringement is not based upon a product that actually exists and can be compared to the claim limitations. Rather, the "infringement action is a hypothetical case that asks the factfinder to determine whether the drug that will be sold upon approval of the ANDA will infringe the asserted patent." In re Brimonidine Patent Litigation, 643 F.3d 1366, 1377 (Fed. Cir. 2011). "This determination is based on consideration of all the relevant evidence, including the ANDA filing, other materials submitted by the accused infringer to the FDA, and other evidence provided by the parties." Abbott Laboratories v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002). The focus of the inquiry, however, remains the product "that is likely to be sold following FDA approval." Id. Further, "[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." Id. (citing Bayer, 212 F.3d at 1249-50).

The question of whether the description in Apotex's ANDA "directly addresses" the issue of infringement substantially impacts the Court's approach, and has particular significance upon the probative value of Cephalon's testing of Apotex's Canadian product. In considering this issue, two cases from the Federal Circuit are instructive: Glaxo v. Novopharm, Ltd., 110 F.3d 1562 (Fed. Cir. 1997) (looking beyond the ANDA to testing of the biobatch to resolve the question of infringement), and Bayer AG, 212 F.3d 1241 (limiting the infringement inquiry to the ANDA itself).

In Glaxo, the Federal Circuit considered whether Novopharm's efforts to bring to market a generic version of Glaxo's anti-ulcer medication, Zantac®, infringed Glaxo's patent on a particular

form ("Form 2") of the active ingredient, ranitidine hydrochloride (RHCl). RHCl was known to exist in at least two forms (Form 1 and Form 2), and often a method of manufacturing the chemical would result in both forms being present. Novopharm sought to gain FDA approval to market a generic form of the drug pursuant to an ANDA that specified that its product would contain at least 90% of Form 1 RHCl, with the other 10% being made up of impurities which could include Form 2 RHCl. In finding that Glaxo had failed to prove infringement, the district court considered testing that was conducted on Novopharm's product which demonstrated that it did not in fact contain any Form 2 RHCl. Id. at 1566.

Glaxo argued it was error for the district court to consider evidence outside of the ANDA, and urged that the district court should have found infringement because the ANDA's broad scope permitted Novopharm to manufacture an infringing product. Id. at 1567. The Federal Circuit rejected this argument, ruling that the relevant inquiry was not what Novopharm *could* produce pursuant to its ANDA, but what it was *likely* to produce. Id. at 1568. The Court stated that normally the ANDA specifies a "well-defined compound," and the question of infringement is "usually straightforward" and "properly grounded in the ANDA application and the extensive materials typically submitted in its support." Id. at 1569-70. However, Novopharm's ANDA failed to address the question of infringement because it was broad enough to include both a product that contained no Form 2 RHCl, and one that contained 10% Form 2 RHCl. Thus, it was unclear from the ANDA whether Novopharm's product was likely to contain any Form 2 RHCl, thereby infringing Glaxo's patent. Id. Under these circumstances, it was proper for the district court to expand its inquiry beyond the ANDA, and consider "the materials submitted by Novopharm to the FDA, and other pertinent evidence provided by the parties." Id. Because testing of the biobatch demonstrated that

no Form 2 RHCl was present in Novopharm's product, the district court's finding of non-infringement was upheld. Id.

Although Glaxo allowed for examination of product testing, the Federal Circuit Court subsequently made clear in the Bayer case that where the ANDA does address the question of infringement, evidence outside of the ANDA should not be considered. In Bayer, Elan, the generic drug manufacturer, was sued for submitting an ANDA which allegedly infringed Bayer's patent claim of a pharmaceutical composition containing nifedipine[9] crystals with a specific surface area (SSA) of 1.0 to 4 m^2/g.[10] Bayer, 212 F.3d 1241. In affirming the district court's grant of summary judgment, the Federal Circuit stated that the ANDA at issue, which required "that the SSA of its nifedipine crystals be at least 5 m^2/g within five days prior to manufacturing," "mandate[d] a finding of no literal infringement." Id. at 1248-1249.

Bayer offered two arguments as to why summary judgment was inappropriate despite the specification in the ANDA. First, it argued that there were "genuine issues of material fact as to whether Elan [would] be able to comply with its SSA specification." Id. at 1248. Second, Bayer argued that the ANDA did not specify the SSA of the crystals just before being "mixed into tablets," and certain evidence showed that the "crystals grow over time before being mixed into tablets, thereby causing the SSA of the crystals to decrease." Id. The Federal Circuit disagreed with Bayer's first argument, stating that "Elan is bound by this specification" and could face severe penalties if it marketed a product that did not comply with it, including an injunction, criminal sanctions and the

[9] "Nifedipine is a compound that acts on the body's circulation—a coronary vasodilator—and is used to control such medical conditions as high blood pressure." Bayer, 212 F.3d at 1245.

[10] Specific surface area "is defined as the total surface area of the particle divided by the particle's weight." Bayer, 212 F.3d at 1245 n. 3.

seizure of the unapproved drug. Id., at 1250. Regarding Bayer's second argument, the Court found it was insufficient to allege that *some* decrease in SSA occurred, particularly where Bayer did not allege, or produce any evidence to show, that the decrease was sufficient to bring the SSA within the claim limitation. Id. at 1249.[11]

When Bayer and Glaxo are considered together, a number of principles relevant to our determination emerge. First, the Federal Circuit has made it clear that the focus of the infringement inquiry under § 271(e)(2)(A) is on the product that is likely to be produced pursuant to the ANDA. As such, we must begin with the ANDA itself, and consider how the specifications it sets forth address the claim limitations in the patent. As in Bayer, where those specifications "directly address" the question of infringement, the inquiry need not proceed any further. However, where, as in Glaxo, the specification in the ANDA leaves open the possibility of infringement by describing a product or a range of products which may, or may not, infringe upon the claim limitations, the court may consider other evidence to determine what product the applicant is "likely" to produce pursuant to its ANDA. That evidence can include "materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder." Bayer, 212 F.3d at 1248-49.

A. Does Apotex's ANDA Directly Address the Question of Infringement?

Whether the particle size limitation in Apotex's ANDA answers the question of infringement depends principally upon Cephalon's allegations and evidence regarding the effect of the comilling step. Relying upon the testimony of its experts, Cephalon contends that milling reduces the diameter

[11]In fact, the evidence produced by Bayer indicated that the decrease was not sufficient, showing "at best, a decline in SSA from 5.09 m^2/g to 4.91 m^2/g over a six day period." Bayer, 212 F.3d at 1249 n. 6.

of the modafinil particles to an infringing size.[12] Because Apotex's ANDA requires that the milling step occur after particle size is measured, Cephalon argues that Apotex's ANDA fails to "directly address" the question of infringement, and thus, under Glaxo, other evidence should be considered—namely the particle size testing of Apotex's Canadian product.

Apotex disagrees and responds that because the particle size specification in its ANDA requires that at least 20% of the modafinil particles be greater than 220 μm, this case is exactly analogous to Bayer, and the Court should look no further than the ANDA to answer the question of infringement. Although Apotex concedes that the milling step has the potential to reduce particle size (albeit not enough to bring its product within the claim limitations), it asserts that measuring the particle size of bulk API prior to the manufacturing process is "conventional in the pharmaceutical industry" even when that process includes a milling step. As evidence of this "convention," Apotex points out that the claim limitations in Cephalon's patent are themselves based upon particle size measurements of bulk API. Apotex therefore asserts that the "pre-processing API particle size measurement is still the 'particle size' of the final product," and Bayer dictates a finding of non-infringement based solely upon the ANDA specification.

While Apotex urges that the specification in its ANDA makes our analysis straightforward,

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[12]Cephalon also argues that the particle size testing on the biobatch submitted in conjunction with Apotex's ANDA was skewed to overstate particle size because the preparation techniques failed to completely diffuse agglomerates, and the testing would have counted those larger agglomerates as individual particles. (Cephalon Post Tr. Br., p. 6.) However, the specification in the ANDA, not the testing of the biobatch, is the focus of the infringement inquiry. Bayer, 212 F.3d at 1249. Moreover, to the extent this argument is raised to challenge Apotex's ability to comply with the specifications in its ANDA, that argument was expressly rejected in Bayer. Id. at 1249-50. Were Apotex to market a product that did not comply with its ANDA, and infringed Cephalon's patent, it would be subject to severe civil and criminal sanctions as well as an infringement action under 35 U.S.C. § 271(a). Id.

we believe, as the Court did in Glaxo , that "the ultimate question of infringement is not so simple." Glaxo, 110 F.2d at 1569. At first blush, because of certain similarities between this case and Bayer, it is tempting to follow Apotex's lead and analyze this case solely under Bayer. In both cases the ANDA contains a particular specification with regard to the characteristic relevant to infringement (SSA in Bayer, particle size here), and in both cases the ANDA's specification appears on its face to preclude infringement. In Bayer, Elan's specification required that the SSA be greater than 5 m^2/g, where Bayer's patent claimed particles with an SSA between 1 and 4 m^2/g. Similarly, Apotex's ANDA specification requires that at least 20% of particles have a diameter greater than 220 µm, and Cephalon's patent claims a product wherein, at most, 5% of modafinil particles have such a diameter. Further, in both cases the patentee pointed to a process that occurred after measurement which had the potential to affect the characteristic at issue. In Bayer, it was the five days passage of time between measurement of SSA and tabletting. Here, it is the milling process described in Apotex's ANDA.

Despite these similarities, we conclude that several key factors distinguish this case from Bayer. First, Apotex's position that what occurs during the manufacturing process is irrelevant because it is customary to refer to the "particle size" of a tablet based upon measurement taken on the bulk API is squarely at odds with the patent's claim of a "pharmaceutical composition" of defined particle size. Indeed, Apotex has admitted that a "pharmaceutical composition" refers to the final tablets, not the bulk API. (N.T. 7/14/11, p. 140 (Apotex's Counsel); N.T. 7/19/11, pp. 148-49 (Beach).) Regardless of whether the custom in the pharmaceutical industry is to refer to the "particle size" of a drug as the particle size measurement taken before processing, the plain language of the patent must take precedent with regard to the infringement inquiry. Interactive Gift Express, Inc.

v. Compuserve Inc., 256 F.3d 1323, 1331 (Fed. Cir. 2001) (citing 35 U.S.C. § 112).

Further, we cannot ignore Apotex's milling process and Cephalon's allegation that this process could reduce particle size to such an extent so as to bring the final tablet within the particle size claims of its patent. Similar allegations were not made in Bayer. See 212 F.3d at 1249 ("Significantly, Bayer does not allege that within five working days, the nifedipine's SSA will decrease . . . to a literally infringing size"). Importantly, the Court's conclusion in Bayer that the ANDA at issue "directly addressed" the question of infringement was dependent, in part, upon the absence of an allegation that the time between measurement of SSA and tabletting was sufficient to bring the product within Bayer's patent. Id. Indeed, the evidence in Bayer definitively showed that the reduction in SSA was not enough to bring the product within the claim limitation. Id. at 1249 n. 6. No such evidence exists here, and Cephalon alleges that the milling step is sufficient to reduce particle size to an infringing level.

Given these circumstances, we conclude that limiting our analysis to Apotex's ANDA would be inappropriate. Consequently, we will consider whether the evidence offered by Cephalon demonstrates that, as a result of the milling step, the drug likely to be produced pursuant to Apotex's ANDA will infringe the particle size limitation in Cephalon's patent.[13] This evidence consists of the results of the particle size testing performed by Cephalon on Apotex's Canadian modafinil product undertaken by Drs. Van Campen and Bugay, and the opinion of Dr. Antonietti regarding the effect of the Quadro Comil used in Apotex's ANDA process.

[13] This conclusion also decides Apotex's motion to preclude the testimony of Cephalon's experts regarding the testing conducted on modafinil tablets manufactured by Apotex for sale in Canada. (Doc. No. 470.) In that motion, Apotex argues that this testimony is irrelevant because its ANDA resolves the question of infringement. For the reasons explained herein, we disagree and deny Apotex's motion.

B. Testing of the Canadian Tablets

The principal evidence presented by Cephalon as support for its infringement argument is the particle size testing that was conducted on a modafinil product that Apotex markets and sells in Canada. Apotex strenuously argues that Cephalon's testing is unreliable because of deficiencies in Dr. Van Campen's protocol and its disparate results. Apotex also asserts that this testing is irrelevant because the Canadian tablets were manufactured pursuant to a different particle size specification and are not representative of what is likely to be produced pursuant to its ANDA. We address each of these arguments in turn.

1. The Reliability of the Canadian Testing

Apotex first asserts that Cephalon's testing of their Canadian modafinil tablets is unreliable, primarily because certain steps in Dr. Van Campen's protocol likely resulted in both the loss of particles and a reduction in particle size. While the Court finds some of Apotex's criticism of Dr. Van Campen's protocol to be well grounded, we are unprepared to definitively proclaim any particular aspect of the protocol to be unreliable.

Apotex's critique of the particular steps in Dr. Van Campen's protocol was based primarily on the testimony of Dr. Beach, who criticized the loss of particles, particularly during the washing step. Dr. Beach opined that the loss of particles was demonstrated by the amount of modafinil recovered in each sample. (N.T. 7/19/2011, pp. 85, 112-13.) Dr. Van Campen, however, testified that very few particles would have been lost during washing, and that the difference between the amount of modafinil recovered and the amount expected to be recovered was likely due to variation within the tablets themselves, rather than any defect in her protocol. (N.T. 7/12/2011, pp. 96-97, 122.)

Dr. Beach further asserted that the sonication steps, which involved shaking the modafinil to break apart the tablets, would likely also break apart the actual modafinil particles, resulting in a smaller particle size distribution. (Id. p. 91.) However, this testimony was also refuted by Drs. Van Campen and Bugay. (N.T. 7/12/2011, pp. 97-99; N.T. 7/13/2011, p. 55.) Further, it is difficult to reconcile Dr. Beach's opinion that sonication would fracture modafinil particles with his opinion that the milling step, during which modafinil particles collide with metal impellers rotating at 900 RMP, does not have sufficient energy to fracture the same particles. (See N.T. 7/19/2011, p. 50.)

Additionally, Dr. Beach's potential bias, which was discussed in the Court's invalidity opinion, cannot be ignored. (See Am. Invalidity Mem. Op., pp. 6-7, ¶¶ 16-17.) His decade-long service as President and member of the Board of Directors at a subsidiary of Apotex, along with the $1 million he received in severance pay in 2006 and his continued contingent financial interest in Apotex's profitability, all give the Court considerable pause as to how much weight should be afforded to Dr. Beach's opinions. When his potential bias is considered together with the testimony of Cephalon's experts and their qualifications, the arguments presented by Apotex do not convince us that any particular part of Dr. Van Campen's protocol can be deemed unreliable.

Apotex does, however, make a compelling argument that the large variation in Dr. Bugay's test results demonstrates that Cephalon's testing, as a whole, is not a reliable basis for the conclusion that 95% of the modafinil particles in Apotex's Canadian product are smaller than 220 μm. A careful examination of Cephalon's test results amplifies this conclusion.

As detailed above, in order to obtain a diameter which included 95% of the modafinil particles in each sample, Dr. Bugay divided the samples into three "preps" and tested each prep three times with the Hiac-Royco. He then averaged these nine tests for each sample, and found that

Samples 4, 5, and 6 fell within the claims of the RE '516 patent. As Apotex points out, a great deal of variation exists between the average 95% cumulative values[14] of the six samples. Indeed, the values range from 158.9 µm for Sample 4, to 285.0 µm for Sample 2.

Cephalon responds by pointing to Dr. Bugay's explanation that these differences were due to variation between the modafinil tablets that Cephalon purchased rather than to any error in his or Dr. Van Campen's testing. (N.T. 7/13/2011, pp. 44-46.) Dr. Bugay explained that the amount of variation was not at all unusual, even in light of the pharmaceutical industry's efforts to produce a consistent product. (Id.)

However, Dr. Bugay's explanation fails to account for the significant variation between the nine test results that formed the basis for the average 95% cumulative value of each sample. As discussed above, each sample was divided into three "preps," and each "prep" was tested with the Hiac-Royco three times, for a total of nine results. These nine results, which were averaged to produce the average 95% cumulative value for each sample, varied greatly. The table below sets forth the 95% cumulative value for each of the nine tests applicable to the three samples that Cephalon contends demonstrate infringement, along with the standard deviation for each sample.

Prep/Test	**Sample 4 (µm)**	**Sample 5 (µm)**	**Sample 6 (µm)**
Prep 1, Test 1	110.1	139.6	167.2
Prep 1, Test 2	120.4	209.8	124.5
Prep 1, Test 3	201.5	207.4	354.6

[14] The term "95% cumulative value" refers to the diameter which is either equal to or greater than the diameter of 95% of the modafinil particles. The final result for each of the six samples tested by Dr. Bugay, which is the average of the 95% cumulative values obtained for each of the nine tests performed, will be referred to as the "average 95% cumulative value."

Prep 2, Test 1	294.1	195.9	100.4
Prep 2, Test 2	155.2	194.0	171.0
Prep 2, Test 3	191.4	356.3	242.9
Prep 3, Test 1	128.3	139.7	164.1
Prep 3, Test 2	110.2	158.6	354.2
Prep 3, Test 3	119.0	196.0	129
Average	158.9	199.9	200.9
Standard Deviation	61.2	64.8	95.8

(Source: PTX-354)

The values obtained in the nine particle size tests performed for each sample demonstrate a large degree of variance. This is illustrated through a simple review of the values obtained in each of the tests for a given sample. For instance, the values obtained for Sample 4 have a low of 110.1 µm and a high of 294.1 µm. Similarly, the values obtained for Sample 5 range from 139.6 µm to 356.3 µm, and the values for Sample 6 range from 100.4 µm to 354.2 µm.

The high degree of variance within each sample is confirmed by the standard deviations. Standard deviation is a statistical measure of variance that is used to measure how much a set of values deviates from its average. Harvey Motulsky, M.D., INTUITIVE BIOSTATISTICS 31 (Oxford Univ. Press, 1995) The greater the variation, the larger the standard deviation will be. Except in unusual circumstances, about two-thirds of the values will fall within one standard deviation of the mean, and approximately 95% will fall within two standard deviations. Id. at 32-33. Applied to Cephalon's test result data, the large standard deviation demonstrates exactly how much variance there was in Dr. Bugay's testing. In Sample 4, only two-thirds of the tests reported a 95% cumulative value between and 97.7 µm and 220.1 µm. Similarly, only two-thirds of the test results

for Sample 5 fell between 135.1 µm and 264.7 µm, and for Sample 6, two-thirds were between 105.1 µm and 296.7 µm.

We conclude that the significant variation in Dr. Bugay's results raises serious concerns about the reliability of the protocol and testing insofar as it relates to the question of infringement. These concerns are compounded by the large degree of variation between tests performed on the same "prep." For instance, the three tests conducted on the first "prep" of Sample 4 produced results that varied by approximately 90 µm. Similar variation is present in the tests conducted on many of the other preps. While we need not rest our conclusions upon a finding that Dr. Bugay's testing is flawed, the variation nonetheless renders Cephalon's testing an unreliable basis for the conclusion that 95% of the modafinil particles in any of Apotex's Canadian tablets are smaller than 220 µm.

2. Is the Canadian Product Tested By Cephalon Representative of What is Likely to be Produced Pursuant to Apotex's ANDA?

In addition to challenging the reliability of Cephalon's testing, Apotex also asserts that such testing is irrelevant because the Canadian tablets are not representative of what is likely to be produced upon approval of its ANDA. Apotex points out that the Canadian tablets at issue were manufactured pursuant to Apotex's Canadian Abbreviated New Drug Submission ("ANDS"), which includes a different particle size specification than the ANDA filed with the FDA. Specifically, the Canadian ANDS contains no upper limit on the percentage of particles that may pass through the 250-micron sieve. (DTX 286; N.T. 7/14/2011, p. 62.) Rather, it simply requires that at least 25% of the particles pass through. In contrast, the ANDA filed with the FDA requires that no more than 80% of the particles pass through a 250-micron sieve. (Id.) As Dr. Antonietti admitted, the ANDS permits the modafinil API to be within the particle size claim of the RE '516 patent prior to milling,

while the ANDA filed with the FDA does not. (N.T. 7/14/2011, p. 68.) Therefore, without other evidence indicating that the two products are identical, it appears that the particle size distribution in the Canadian modafinil tablets is not representative of what is likely to be produced pursuant to the specification in the ANDA.

Cephalon disagrees and argues that despite the different specifications, the Canadian tablets are "identical to what Apotex is likely to sell in the United States." (Cephalon Post Tr. Br., p. 7.) Cephalon supports this argument in two ways. First, it relies upon the deposition testimony of certain Apotex employees that if the ANDA were approved, and the generic modafinil product were marketed in the United States, Apotex would ideally manufacture one pill that would meet both specifications and market and sell the same pill in both Canada and the United States. (Id., pp. 8-9.) Second, in conjunction with both the ANDA and the ANDS, Apotex submitted identical testing performed on the same modafinil API. (Id.) Thus, Cephalon concludes that although Apotex changed the particle size specification in its ANDA to include an upper limit, that amendment "was merely intended to tighten the specification around the same batches of modafinil that Apotex used to justify" the specification in its original ANDA. (Id., p. 8.) Cephalon asserts that the bulk modafinil Apotex intends to use, and the process for manufacturing it into finished tablets, remains the same for both Canada and the United States. For the following reasons, we find neither of these arguments to be convincing.

First, the deposition testimony of Apotex's employees does not demonstrate an intent to manufacture a product in the United States that is identical to what is currently being produced in Canada. Rather, the employees merely testified that, as a general matter, it was Apotex's practice

to try to harmonize the specifications and manufacturing processes for a given drug in as many markets as possible because it was more efficient and cost-effective to sell the same drug in multiple markets. (See Kovacs Dep., pp. 108-13; Dandicker Dep., p. 53; Tao Dep., pp. 270-72.) There was also clear testimony offered that in the event that the Canadian and United States productions cannot be harmonized, different processes will be used for each market. (Dandicker Dep., p. 54.) Further, no employee testified that it was Apotex's intent to use the same bulk API and manufacturing process for its United States and Canadian modafinil products. Indeed, Elisabeth Kovacs, a Director of Analytical Operations at Apotex, testified that she did not know whether the bulk API currently used in Canada would be used for manufacture in the United States. (Kovacs Dep., p. 107.)

In short, the evidence relied upon by Cephalon establishes only that Apotex believed it to be more efficient and cost-effective to manufacture a single drug for sale in multiple markets whenever possible. It does not, however, demonstrate that Apotex intends to use the same bulk modafinil and manufacturing process in the United States that it currently uses in Canada.

Cephalon also posits that the Canadian tablets are representative because the same testing was submitted in conjunction with both the ANDA and the ANDS. This argument misconstrues the role of the biobatch in the context of the infringement inquiry. Apotex admits that the same biobatch was used and tested in conjunction with both the ANDA and the ANDS. Nonetheless, it is the specification contained in the ANDA that controls what Apotex must manufacture, not the biobatch. See Bayer, 212 F.3d at 1249. Indeed, as the Federal Circuit has noted, "even if the biobatch falls within the scope of the claims, the Act specifically indicates that such actions . . . cannot constitute infringement." Id. We recognize that in certain circumstances, the biobatch may be evidence of what will be produced pursuant to the ANDA. See Glaxo, 110 F.3d 1562. However,

the "focus of the inquiry . . . is on the product that will be sold after the FDA's approval of the ANDA, not on the biobatch that is produced to facilitate approval." Bayer, 212 F.3d at 1249 (internal citations omitted). The mere fact that the Canadian and United States specifications were supported by testing on the same biobatch does not demonstrate that Canadian tablets purchased years later are representative of what is likely to be produced pursuant to the ANDA where the particle size specification differs from the Canadian one.

Finally, Cephalon's argument that the particle size distribution in the Canadian tablets demonstrates the extent of reduction caused by the milling process would also require us to assume that Apotex's Canadian API conforms to the biobatch, rather than simply to the specification in the ANDS. If the Canadian tablets that Cephalon tested had been made from the biobatch, the particle size distribution would be known both before and after the milling process, and a reliable conclusion could be drawn about the effect of milling. However, the Canadian tablets were manufactured years later, and, consequently, there is no evidence about the particle size distribution of the API from which they were manufactured. Although Cephalon cannot be faulted for failing to test tablets made from the biobatch because those samples expired before substantial discovery had begun in this case, the Court cannot assume that the API from which the Canadian tablets were manufactured was identical to the biobatch. Rather, all that is known is that somewhere between 25% and 100% of the modafinil particles were smaller than 220 μm.

Considering the evidence presented, and the difference in particle size specifications in the ANDA and the ANDS, we decline to conclude that the Canadian tablets are representative of what is likely to be produced pursuant to the ANDA.

C. Dr. Antonietti's Opinion Regarding the Effect of the ANDA's Milling Step

Cephalon also points to Dr. Antonietti's opinion as support for the proposition that the milling step implemented by Apotex would result in modafinil that infringed the claims related to particle size in the RE '516 patent. Dr. Beach disputed these assertions and opined that the milling step would not significantly reduce particle size.

Dr. Antonietti testified that, based upon his review of relevant documents, and his knowledge of pharmaceutical manufacturing, the milling process described in the ANDA would lead to a "significant" reduction in particle size. (N.T. 7/13/2011, p. 156.) This reduction would be caused by the modafinil particles contacting either the impellers inside of the mill, or the wall of the mesh screen. (Id., pp. 164-65.) Dr. Antonietti stated that as the impellers spin around the inside of the mill, mixing the modafinil that is passing through the screen, they will contact the modafinil with enough energy to break apart the crystalline structure of those particles, resulting in smaller particles post-milling. (Id.) Similarly, he testified that some of the particles would contact the mesh screen with sufficient energy to break apart their crystalline structure. (Id., pp. 168-170.) Dr. Antonietti asserted that this could occur even with particles that are smaller in diameter than the 457-micron holes in the comil called for in Apotex's ANDA because the particles may hit the screen at an angle rather than pass straight through the holes—a concept referred to as "apparent hole size." (Id.)

According to Dr. Antonietti, the contact between the particles and both the impellers and the mesh screen would cause a "very significant particle size reduction." (Id., p. 169.) He acknowledged that the extent of this reduction depended upon "practically everything," including "rotation speed, the type of [impellers], [and] the size between the [impeller] and the screen." (Id., p. 168.) He could not, however, quantify the amount of the reduction.

Dr. Beach disputed Dr. Antonietti's conclusions regarding the effect of the milling step in the ANDA. According to Dr. Beach, the principal purpose of this step is to break up any agglomerates that might be present in the bulk powder. As Apotex's purpose was not to reduce particle size, Dr. Beach stated that Apotex used rounded impellers rather than beveled ones, a round-hole screen rather than a "grater" screen (which he stated "resembled a cheese grater"), and set the impellers to rotate at only 900 RMP, less than a third of their 3000 RPM capability. (N.T. 7/19/2011, pp. 51-53.) Considering these factors, Dr. Beach opined that the milling step introduced insufficient energy to reduce particle size to a significant degree. (Id., p. 50.) He also criticized Dr. Antonietti's calculation regarding "apparent hole size," stating that it was based upon figures in a sales brochure and failed to account in any way for the particular characteristics of Apotex's milling process, including the choice of impeller, the choice of screen, and the impeller speed. (Id., p. 54.) He opined that, even accounting for apparent hole size, a 300-micron particle would "certainly . . . go through that comil without being reduced in particle size." (Id., p. 61.) Dr. Beach noted that in the biobatch submitted in conjunction with Apotex's ANDA, 12.45% of the particles were between 250 and 300 microns in diameter. (Id., pp. 59-60.) In his opinion, all of these particles would pass through the comil intact, and he therefore concluded that the number of these particles alone precluded infringement.

There are factors which weigh in favor of, and against, crediting either expert's testimony regarding the effect of the milling process in Apotex's ANDA. Both Dr. Antonietti and Dr. Beach are well-qualified, appeared knowledgeable and have a great deal of experience in the pharmaceutical industry. However, Dr. Antonietti's reliance upon a manufacturer's brochure as evidence of apparent hole size, and as a basis for his calculations, provides some reason to question

the accuracy of his conclusions. Moreover, his experience with the Quadro Comil is not nearly as extensive as Dr. Beach's. Conversely, Dr. Beach's potential bias arising from his prior and ongoing financial interest in Apotex creates some skepticism regarding his opinions. Further, Dr. Beach's opinion that the milling step would impart insufficient energy to break apart the modafinil particles is incongruous with his opinion that Dr. Van Campen's low-energy sonication would fracture the particles.

We need not resolve these differing opinions in light of the Court's conclusions regarding the Canadian testing. While Cephalon asserts that Dr. Antonietti opined that Apotex's milling step would produce modafinil within the claimed particle size distribution "[b]ased upon his review of materials including Apotex's ANDA, technical documents supplied by the manufacturer of the Quadro Comil that is used in Apotex's manufacturing process, and scientific literature" that description of his testimony is imprecise. Rather, without reference to the Canadian testing, Dr. Antonietti could only establish that milling would "lead to a significant reduction" and result in particles that are "much smaller than the screen size." (N.T. 7/13/2011, pp. 156, 163.) In fact, Dr. Antonietti admitted that, because of the milling step, "particle size will be significantly smaller and you don't know how small it is." (Id., p. 176.)

Dr. Antonietti did opine that "this is a case of literal infringement," (N.T. 7/13/2011, p. 143), but, this opinion was based upon his acceptance of the testing of Apotex's Canadian product by Drs. Bugay and Van Campen. Dr. Antonietti stated that their testing was a "very important basis" of his opinion. (Id., p. 182.) In fact, when asked specifically whether Apotex's manufacturing process was "likely to result in a particle size distribution" that infringed the claims of the RE '516 patent, Dr. Antonietti's response was that infringement had "been proven by the expert reports of Dr. Van

Campen and Dr. Bugay." (Id., p. 173.) He further testified that he found Dr. Van Campen's protocol to be sound, Dr. Bugay's particle size measurement to be accurate, and the Canadian tablet to be "identical to what Apotex proposes to sell in the United States." (Id., pp. 182, 183.) For the reasons explained above, we do not agree that the Canadian testing has the significance that Dr. Antonietti attached to it in forming his infringement opinion. While it may very well be the case that milling substantially reduces particle size, Dr. Antonietti could not provide any basis, independent of the particle size testing of Apotex's Canadian product, to conclude that the milling step described in Apotex's ANDA would reduce particle size enough to bring the final tablet within the claims of the RE '516 patent.

V. Conclusion

For the reasons stated above, the Court finds that the milling step in Apotex's ANDA justifies our consideration of evidence outside of the ANDA. However, Cephalon has not produced sufficient evidence to demonstrate that the milling step reduces particle size to such a degree that the pharmaceutical composition produced pursuant to Apotex's ANDA is likely to be a pharmaceutical composition of modafinil wherein 95% of the modafinil particles have a diameter smaller than 220 μm. Accordingly, the Court concludes that Cephalon has not proven infringement by a preponderance of the evidence.

Our Order follows.